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Immunization and Aging: a Learning Process in the Immune Network

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The immune system can be thought as a complex network of different interacting elements. A cellular automaton, defined in shape-space, was recently shown to exhibit self-regulation and complex behavior and is, therefore, a good candidate to model the immune system. Using this model to simulate a real immune system we find good agreement with recent experiments on mice. The model exhibits the experimentally observed refractory behavior of the immune system under multiple antigen presentations as well as loss of its plasticity caused by aging.

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The special capability of the immune system is pattern recognition and its assignment is to patrol the body and guard its identity. The main cells responsible for the immune response against any attack by antigens (virus, poison, etc.) are the white blood cells called lymphocytes. Each lymphocyte carries on its surface the order of 10^5 molecular receptors and the immune system is able to produce the order of 10^{11} different types of molecular receptors. One of the main classes of lymphocytes are the B cells which produce antibodies with the same molecular shape as those of its molecular receptors. Each molecular receptor (or antibody) is able to recognize and to be recognized. This immune recognition can lead either to a positive response, which generates cell proliferation, cell activation and antibody secretion, or to a negative one that results in tolerance or suppression.

In 1974 Niels Kay Jerne[1] proposed a theory which compares the immune system to a self-regulated multiconnected functional network. This functionally connected network, generated by the (lock-key) interactions among the elements of the immune system, is self-regulated by the dynamics of activation and suppression; some populations decay and new ones grow, but there is no percolation of the information through the entire immune system. The immune memory may be a consequence of network interactions. Some experiments[2,3] suggest that only 20% of the lymphocytes are connected, whereas their majority are small resting cells, able to respond to any antigen.

We have simulated recently[4] a modified version[5] of a cellular automaton model proposed by Stauffer and Weisbuch[6], which, in turn, was based on one introduced by De Boer, Segel and Perelson[7]. Although the previous studies have shown that this model can exhibit stable and chaotic behaviors, none of them are interesting from the immunological point of view. Our simulations have demonstrated that in the transition region, between those behaviors, we obtain a multiconnected functional network whose emergent properties reproduces many of the properties of the temporal evolution of the immune repertoire[4].

The elements of the automaton are associated with points in shape-space[8]. Each point on a d-dimensional space corresponds to the shape of a molecule (associated with a B cell receptor or antibody). Every one of the d coordinates describes one of many factors involved in the immune pattern recognition, such as geometrical shape, electric charge, hydrophobicity etc. To each site i we associate an automaton of three states, representing the population (concentration) of the corresponding receptor: low - or non-activated ($B_i = 0$), intermediate ($B_i = 1$) and high - or excited ($B_i = 2$). Site i interacts with $2d + 1$ sites: its mirror image $-i$ and the nearest neighbors of the mirror image (representing imperfect lock-key interactions). For each site we define a field h_i that represents the concentrations of complementary receptors,

$$h_i = \sum_{j(i)} B_{j(i)} \tag{1}$$

where the sum runs over the $2d + 1$ sites $j(i)$ that influence the site i. The update rule of the automaton is based on a dose response function which describes the receptor crosslinking involved in B cell activation[5–7]. There is a minimal dose (θ_1) of antigen/or antibody excitation that elicits the specific response, but for a high dose of excitation (greater than θ_2) the response decreases (suppression). The rule is

$$B_i(t+1) = \begin{cases} B_i(t) + 1 & \text{if} \quad \theta_1 \le h_i(t) \le \theta_2 \\ B_i(t) - 1 & \text{otherwise} \end{cases} \tag{2}$$

but no change is made if it would lead to $B_i = -1$ or $B_i = 3$.

This model exhibits a transition from stable to chaotic regimes for $d \ge 2^5$, depending on the activation threshold (θ_1) and the width of the activation interval of the

window $(\theta_2 - \theta_1)$. In the stable region the system always evolves to fixed points or short limit cycles, with very low percentage of activated sites, whereas in the chaotic region most sites are excited, corresponding to a non-healthy state. None of these behaviors corresponds to the dynamical picture of the functional connected network suggested by Jerne. In the transition region (whose location depends on d[5]) we did observe, however, emergent complex behavior which is appropriate to describe a self-regulated multiconnected network[4]. We have also shown that memory comes from the dynamics of the system and can be described as the ability of the system to adapt to changes provoked by excitations (antigen presentations).

We use this model to simulate the main features observed in some recent experiments concerning immunization and the effects of aging on the immune response of mice[9–11]. Since until now there is only limited evidence supporting the existence of the immune network[2,3] but no conclusive proof, our simulations may provide the much needed connections between the available experimental results and the Jerne theory.

Verdolin[9] subjected young (8 weeks old) mice to a first immunization, and 14 days afterwards to 9 consecutive immunizations with intervals of one week between them. The specific antibodies are measured 7 days after each antigen presentation. The protocol used for immunization consist of intraperitoneal injection (boosters) of a specific antigen (OVA). Verdolin's results (for a group of 6 mice) show (see Fig 1) the specific antibody counts as a function of the presentation with all doses counted relative to the first immunization response. The results show a fast increase from the first to the fourth presentation with a consecutive saturation of the response. This is interpreted from the immunological point of view as a refractory behavior of the immune system, meaning that after few presentations there is a saturation of the level of antibody counts, a fact that can not be explained only by clonal selection theory for the immune system.

The second experiment we discuss in this paper concerns the effects of aging on the immune responsiveness. According to the results obtained by Lahmann *et al.*[10] and, later, by Faria *et al.*[11] for young (8 weeks) and old (25 weeks) mice, after the first immunization the response of the young mice achieves much higher levels (in the antibody counts) than the response generated by the old ones, indicating some rigidity of the system, acquired during the aging process. In other words, there is a loss of responsiveness (see the insert of Fig 1).

We set out to test whether the model (1-2) is able to reproduce the experimental findings, of saturation and aging described above. We used the following initial distribution for the B variables: $(1 - x)$ of $B = 0$, and $\frac{1}{2}x$ of $B = 1$ and 2. All our simulations were performed at the transition region for a three-dimensional lattice with $L = 50$; the results are qualitatively the same as those obtained with $L = 100$ and for higher dimensions[4]. We chose $x = 0.26$ and used the activation interval according to our previous studies. In order to study the effects of a given antigen presentation we proceed as follows: a system, prepared as described above, was allowed to evolve according to the rules (1-2); this was used as our "control" group. In a replica of the same initial system the antigen presentation is simulated by introducing "damage"[12]: randomly chosen regions of receptor populations in the $B = 0$ state were flipped to the activated state$(B = 2)$[4]. This flip simulates the exposure to antigen indirectly, by the activation or the increase of the concentration of specific clones (receptors) that are able to recognize this antigen. The evolution of the control system and the damaged copy was then compared by measuring the Hamming distance between them, to study the effects of the antigen presentation. In the case of one or two antigen presentations[4] the results indicate that under perturbation the multiconnected network expands and relaxes in few time steps, following an aggregation/disaggregation dynamics which adapts the system to the new conditions, including some sites of the damaged regions in the next configuration of the functional network.

In this work we discarded in all simulations the initial 1000 Monte Carlo Steps (MCS)- a step consists of one update of all sites. At this point(considered to be equivalent to the "birth"of the immune system) we start to produce at random antigen presentations of different types and sizes, with different, randomly chosen time intervals between them. This introduced noise simulates a real immune system exposed to many antigens, present in the environment in which the system lives and is ingested in food, etc. We adopted the arbitrary time scale of 5 MCS corresponding to one day. The noise discussed above was generated by small damages produced at random: the time interval between two consecutive antigen presentations can vary from 1 to 100 MCS $(1 - 20$ days); each antigen presentation can correspond to 1, 2 or 3 damages introduced at different regions of non-activated populations. These regions may have different sizes, varying from 1 to 3 (onion-like) concentric layers (containing 7, 25 and 63 sites respectively) around a central site. The control system and the replica that simulates the immunization process (multiple antigen presentations) were subjected to the same noise, during the entire simulation. The immunization protocol was simulated by damaging 6 layers around a specific site at fixed time intervals of one week (35 MCS), corresponding to the peritoneal injection. This high-dose antigen presentation clearly differentiates the specific antigen presentation from the noise. We performed these sequences of high dose antigen presentations starting at two different times, corresponding to two different ages, 8 weeks (280 MCS) and 25 weeks (875 MCS), in order to study the effects of aging on the immune responsiveness.

In figure 2 we show the results obtained for a sequence of antigen presentations. For each case (different age) our results are averaged over 10 statistically independent samples corresponding to 10 randomly uncorrelated ini-

tial configurations (and different noise).

The specific antibodies counts in the experiments are compared in our simulations to the number of different excited populations involved in the response, which is measured by the time evolution of the total Hamming distance between the "control" and the excited replica. We obtained the same qualitative behavior as the real immune systems shown in figure 1. After few presentations the responses saturate, showing the same refractory behavior as seen in the experiments. Since in the experiments the specific response was measured (corresponding to the antigen that was used), we have also considered, in our simulations, the specific response. To this end we measured the changes on the clones belonging to the damaged region (DR) and its mirror image (M). Saturation is seen also in these regions, as shown in Fig 3, which presents the specific changes in DR, M and the total HD for a single sample (the same behavior was observed in all samples).

The learning process that may occur in the immune network, due to the antigen introduction, results in local changes of the activated clones configurations, and memory is due to the attainment of a new steady state after the antigen challenge disappears. The learning process that may occur due to multiple antigen presentations, leads to the saturation behavior: after a few antigen presentations the system learns how to control the excitation provoked by this antigen and does not need to improve the response anymore. This interpretation is supported by other studies performed for high-dose antigen presentations without noise, that will be published elsewhere. By observing the evolution of the excited sites in the DR and M regions, we saw that after each presentation more sites are included in the functional network. After that, the response will stay the same. The multiple antigen presentation, lead to the saturation of the number of new sites incorporated in those regions and after that the system will always give the same response to this kind of antigen. The aggregation/disaggregation processes guarantee that the subsequent configurations of the network, arrived at after each antigen presentation, include the necessary information about the damage introduced, but still keep only $10-20\%$ of the sites excited, in agreement with the experimental results.

This conclusion is also reinforced by the observation that, the level of saturation and also the time necessary for the system achieve the saturated state will depend on the size and number of damages which simulate the antigen presentation. We have performed the same kind of simulation (immunization procedures) for different sizes of the damages; for small damages (4 layers) the system saturates faster than for big ones (6 layers), since it learns faster about the small damaged regions.

The data shown in the insert of figure 2 corresponds to the saturation values of the Hamming distance difference between "control" and replica as measured for the two different ages (8 and 25 weeks). From those results we conclude that the "older" the system is, the more rapidly it saturates and the less intense is its response. The older system has been exposed to a larger number of different antigens, thus more regions have already been excited, more information has been added to the functional network and the system is more rigid to accept new local changes. Old systems saturate faster than young ones, since less changes are accepted in their dynamics. The rigidity of the system, which increases with age, can be interpreted from the network point of view as a loss of its plasticity. The younger the system the greater its plasticity.

In this work we have shown that the multiconnected functional network obtained in the critical region of a simple cellular automaton model can describe the behavior of a real immune system. The emergent properties of the cooperative behavior found in our simulations are in good agreement with the experimental results exhibited by mice in experiments of immunization and aging. Our results indicate that the Jerne theory as implemented in this model could explain these experimental observations and possibly provide the much needed connection between this theory and the available experiments. The immunization process and the saturation (refractory behavior) observed in the antibody counts are interpreted within the network point of view as the learning process of the immune system and the aging effects are interpreted as the loss of ability to produce new local changes or the loss of plasticity. This work also give support to many conjectures which suggest that the emergent properties exhibited by complex automata, resulting from a dynamical behavior involving adaptive mechanisms are very appropriated to describe biological systems. The use of cellular automata to model the immune responses has been reviewed recently by one of us[13].

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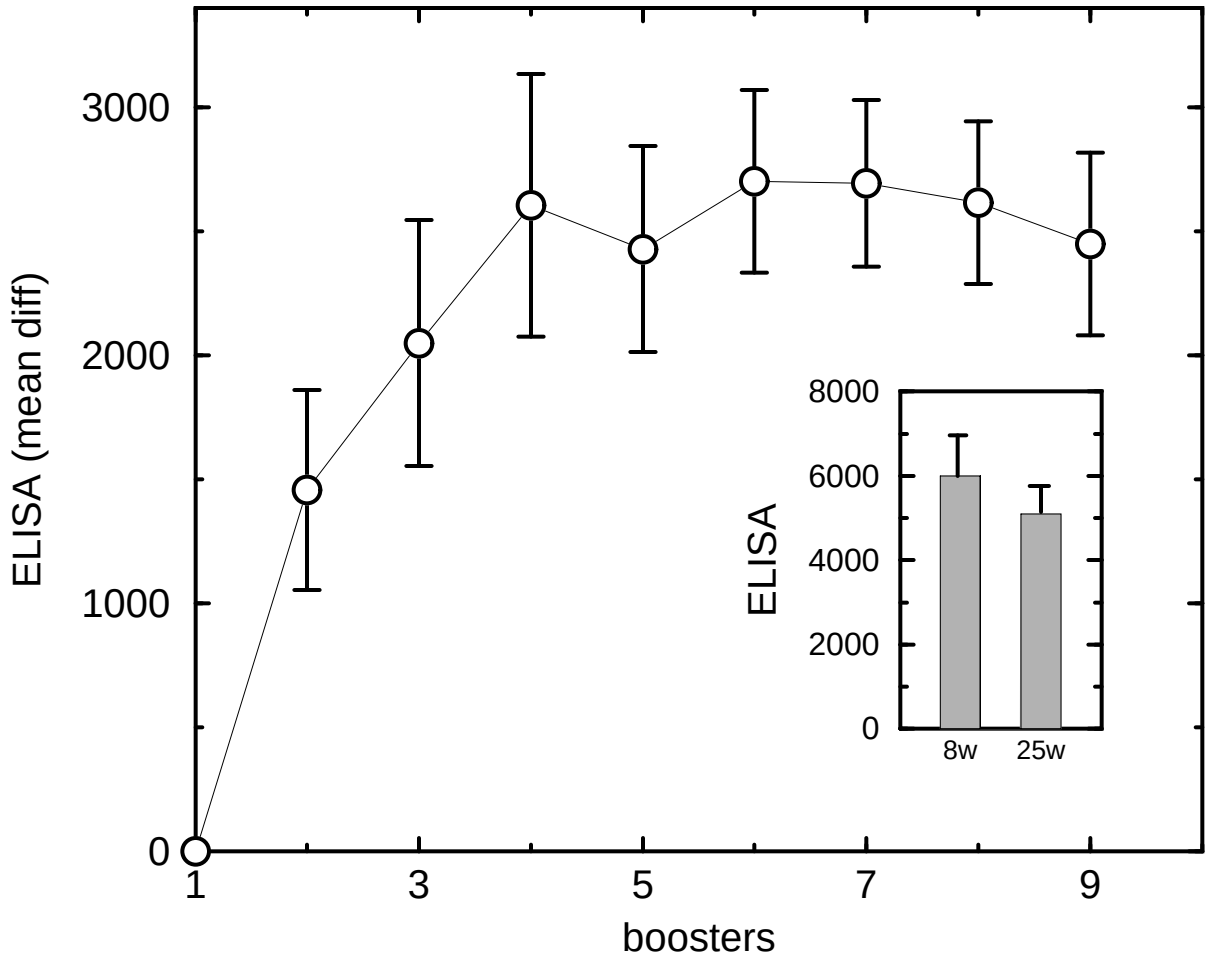
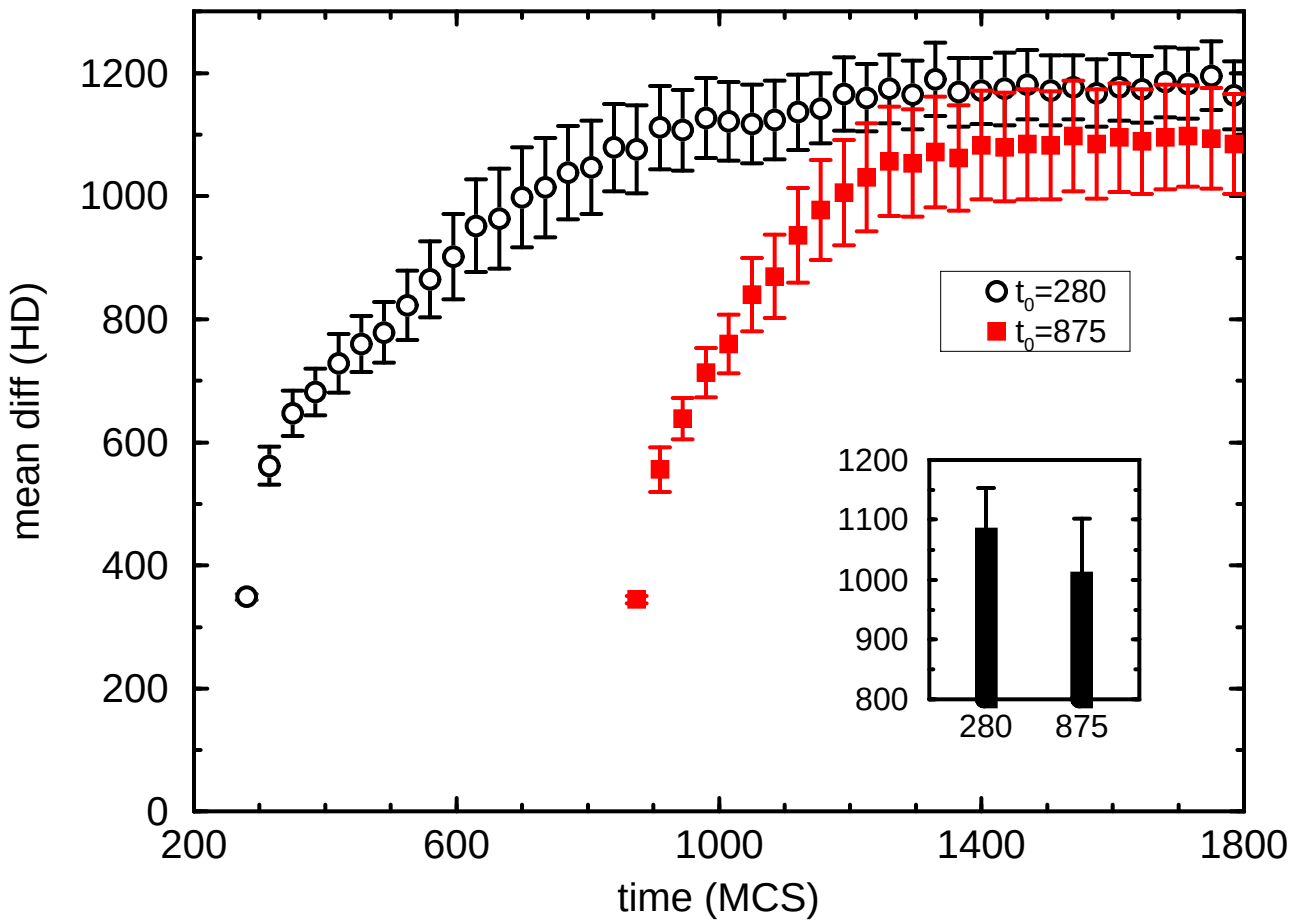
Figure Captions:

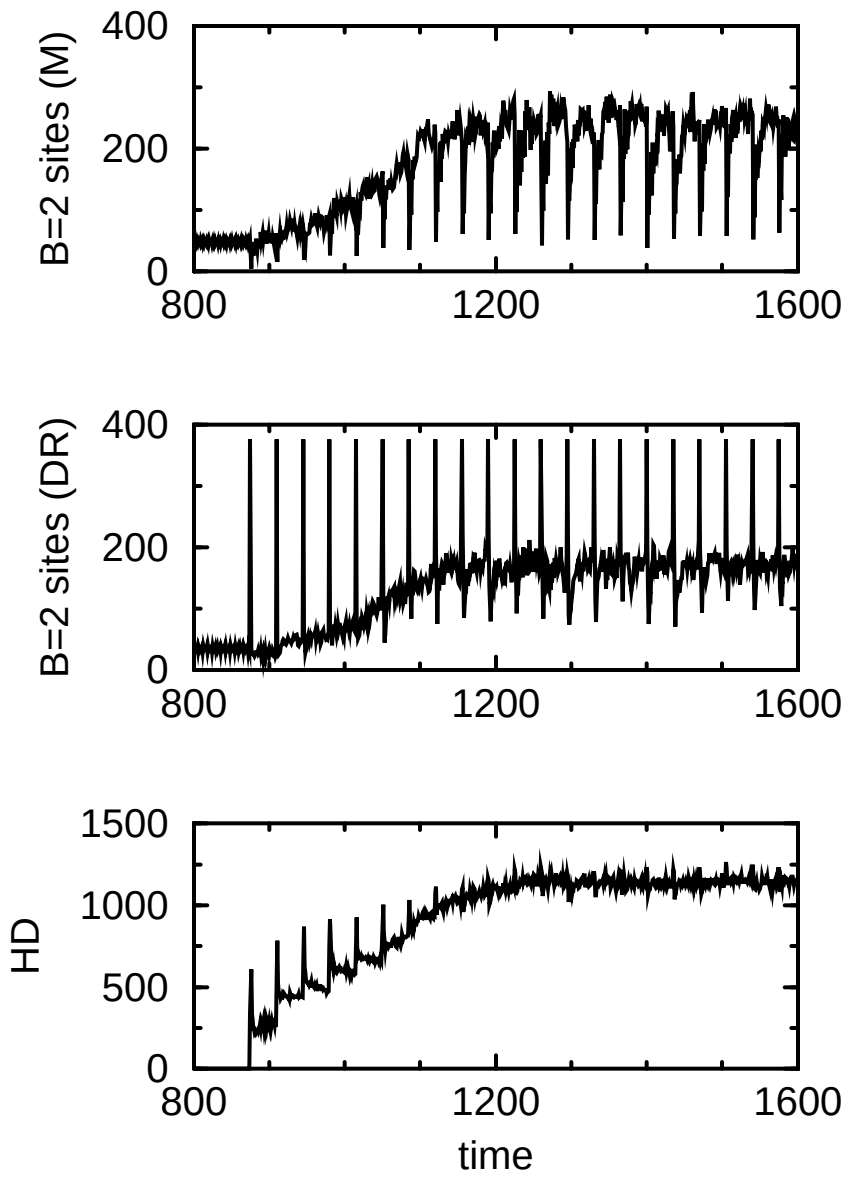
Figure 1: The specific antibody counts as a function of the 9 antigen (OVA) presentations (boosters) for a group of 6 young mice (8 weeks old) with one week of interval between them. All data are normalized by the first response[9]. In the insert we show the effects of aging in the specific antibody counts as a function of the antigen presentation for young (8 weeks old) and old (25 weeks old) mice[11].

Figure 2: The time evolution of the difference between the Hamming distances of "control" group and replica group which was subjected to a sequence of antigens presentation with one week of interval between them. The simulations were performed for two different ages: (circle) starting at $t = 280$ (8weeks) and (square) at $t = 875$ (25 weeks). In the insert we show the mean saturation values for the Hamming distance differences for the two ages considered.

Figure 3: The evolution of the Hamming distance difference between "control" and replica, for one sample, for the damaged region (DR), the mirror image of the damages region (M) and the overall changes on the lattice (HD). This simulation corresponds to the immunization process performed in a 25 weeks old system, by producing a damage of 6 concentric layers (377 sites). The M region corresponds to images and nearest-neighbors of the damaged region.


ELISA (mean diff)
3000
2000
1000
0
1
3
5
7
9
boosters
ELISA
8000
6000
4000
2000
0
8w
25w


mean diff (HD)
time (MCS)
0
200
400
600
800
1000
1200
200
600
1000
1400
1800
t0=280
t0=875
1200
1100
1000
900
800
280
875


B=2 sites (M)
400
200
0
800
1200
1600
B=2 sites (DR)
400
200
0
800
1200
1600
HD
1500
1000
500
0
800
1200
1600
time